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OXIDATIVE STRESS IN CHRONIC KIDNEY DISEASE: MOLECULAR MECHANISMS, GENETIC DETERMINANTS, AND CLINICAL IMPLICATIONS

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Abstract: Background: Chronic kidney disease (CKD) is characterized by progressive renal dysfunction and high morbidity, especially due to cardiovascular complications. Oxidative stress (OS), defined as imbalance between reactive oxygen/nitrogen species and antioxidant defenses, is increasingly recognized as a central pathogenic mechanism in CKD.
Objectives: This review critically evaluates evidence on molecular mechanisms, genetic determinants, clinical consequences, biomarkers, and therapeutic strategies targeting OS in CKD.
Methods: Literature from 2018–2025 was systematically reviewed using PubMed, Scopus, and Web of Science, focusing on reactive oxygen/nitrogen species, mitochondrial dysfunction, NADPH oxidases, uremic toxins, genetic polymorphisms, oxidative biomarkers, and antioxidant therapies.
Results: OS in CKD arises from mitochondrial dysfunction, eNOS uncoupling, NADPH oxidase activation, and accumulation of uremic toxins. Genetic variants in HLA, APOL1, and Nrf2 pathways influence susceptibility. OS promotes renal fibrosis, cardiovascular disease, anemia, and chronic inflammation. Biomarkers of lipid, protein, and DNA oxidation correlate with disease severity. Antioxidant and pharmacological interventions yield mixed clinical efficacy.
Conclusion: OS is a pivotal mediator of CKD progression and systemic complications. Integrating molecular and genetic insights into clinical practice may improve early diagnosis and guide targeted therapies.

Keywords: chronic kidney disease, oxidative stress, mitochondria, genetic polymorphism, cardiovascular complications, antioxidant therapy.

Introduction: Chronic kidney disease (CKD) affects approximately 10–12 % of the global adult population and remains a significant cause of morbidity, mortality, and healthcare cost worldwide. According to the Global Burden of Disease Study, CKD has persistently risen in ranking among leading causes of years of life lost, largely driven by aging populations, diabetes mellitus, hypertension, and chronic inflammatory disorders (GBD Chronic Kidney Disease Collaboration, 2020). Despite advances in diagnostic and therapeutic approaches, CKD progression continues unabated for many patients, primarily due to cardiovascular complications and limited efficacy of conventional interventions.

Traditionally, the pathogenesis of CKD has been attributed to hemodynamic alterations, metabolic derangements, and immune-mediated injury. However, these factors alone do not fully account for the heterogeneity in disease progression and outcomes. In the past decade, oxidative stress has emerged as a central and unifying mechanism linking renal injury, inflammation, genetic susceptibility, and systemic complications in CKD [1].

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Oxidative stress is defined as a state in which production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms endogenous antioxidant defense systems, leading to oxidative damage of lipids, proteins, and nucleic acids. While ROS/RNS at physiological levels contribute to intracellular signaling and defense responses, excessive accumulation results in cellular injury, mitochondrial dysfunction, and apoptosis. The kidneys are particularly vulnerable to oxidative injury due to their high metabolic demand, rich mitochondrial content, and continuous exposure to circulating toxins.

Increasing evidence indicates that oxidative stress is present from early stages of CKD and contributes to disease progression, independent of traditional risk factors. Genetic predisposition, including polymorphisms in antioxidant regulatory pathways, further modulates susceptibility to oxidative injury [5]. A clearer understanding of these mechanisms is essential to develop novel diagnostic and therapeutic strategies.

Methodology of Literature Search: This narrative review was based on a comprehensive literature search of peer-reviewed articles published between January 2018 and May 2025. The databases searched included PubMed/MEDLINE, Scopus, and Web of Science. Search terms combined were: "chronic kidney disease," "oxidative stress," "reactive oxygen species," "mitochondrial dysfunction," "NADPH oxidase," "genetic polymorphism," "glomerulonephritis," "cardiovascular disease," and "antioxidant therapy." Additional articles were identified by manual search of reference lists from key studies and reviews.
Inclusion criteria were:

1. Original research articles, systematic reviews, and meta- analyses;
2. Studies involving adult or pediatric CKD populations;
3. Studies addressing molecular mechanisms or clinical outcomes related to oxidative stress.

Exclusion criteria included case reports, conference abstracts, non- English publications, and articles lacking relevance to oxidative stress or CKD.
Priority was given to articles published in high- impact journals, such as Kidney International, Journal of the American Society of Nephrology, Clinical Journal of the American Society of Nephrology, Nature Reviews Nephrology, and Clinical Kidney Journal.

Molecular Mechanisms of Oxidative Stress in CKD

Reactive Oxygen and Nitrogen Species in Renal Physiology: ROS (e.g., superoxide anion, hydrogen peroxide, hydroxyl radical) and RNS (e.g., nitric oxide, peroxynitrite) are by- products of aerobic metabolism and participate in signal transduction, host defense, and adaptation to stress. In renal physiology, controlled ROS levels regulate vascular tone, tubuloglomerular feedback, and sodium transport [11]. However, excessive ROS/RNS accumulation triggers oxidative damage to cellular macromolecules, disrupting glomerular and tubular integrity [12].

Mitochondrial Dysfunction and Impaired Bioenergetics: Mitochondria are the main source of ATP production in renal tubular cells and a principal generator of ROS. In CKD, mitochondrial respiration is impaired, leading to electron transport chain inefficiency, leakage of electrons, and excessive ROS production. Studies demonstrate early mitochondrial injury, with altered dynamics (fission/fusion) and defective mitophagy, preceding structural renal damage (Galvan et al., 2017; Che et al., 2019). ROS generated within mitochondria further amplify oxidative injury, promoting tubular atrophy and interstitial fibrosis.

NADPH Oxidase Activation: NADPH oxidases (NOX) are dedicated ROS- producing enzymes. Among the NOX family, NOX4 exhibits high constitutive activity in renal tubular

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epithelial cells and podocytes (Gorin & Wauquier, 2018). NOX4 overexpression correlates with glomerulosclerosis and extracellular matrix deposition. Experimental inhibition of NOX4 attenuates ROS production, reduces fibrosis, and preserves renal architecture, highlighting its pathogenic significance.

Uremic Toxins and Oxidative Imbalance: Progressive loss of renal function leads to accumulation of uremic toxins such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS), which exert direct pro-oxidant effects. These protein-bound toxins are poorly cleared by dialysis and correlate with increased OS and cardiovascular risk. IS induces ROS by activating NADPH oxidase, inhibiting mitochondrial electron transport, and suppressing Nrf2 signaling. Elevated PCS similarly enhances mitochondrial ROS and impairs NO bioavailability [3,9].

eNOS Uncoupling: Endothelial nitric oxide synthase (eNOS) normally produces nitric oxide (NO), a vasodilator with anti-inflammatory properties. In CKD, oxidative degradation of tetrahydrobiopterin (BH4), an essential eNOS cofactor, leads to enzyme uncoupling, resulting in superoxide generation rather than NO. Elevated asymmetrical dimethylarginine (ADMA) levels further inhibit eNOS activity, exacerbating endothelial dysfunction and promoting vascular injury [12,14].

Genetic Determinants of Oxidative Stress

HLA and Immune-Mediated Oxidative Injury: Genetic predisposition significantly modulates OS responses in CKD. Polymorphisms in the human leukocyte antigen (HLA) region influence immune activation, leading to sustained inflammatory reactions and increased ROS production in glomerular diseases. Certain HLA alleles are associated with accelerated progression to end-stage kidney disease in chronic glomerulonephritis [14].

Non-HLA Variants and Antioxidant Pathways: Non-HLA loci involved in antioxidant defense mechanisms play crucial roles in redox regulation. Variants affecting the Nrf2 pathway, which controls expression of key antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), are linked to heightened oxidative damage and inflammation in CKD patients [1].

APOL1 and Oxidative Susceptibility: APOL1 risk variants, prevalent in individuals of African ancestry, contribute to rapid CKD progression through mechanisms involving mitochondrial ROS overproduction, podocyte apoptosis, and impaired autophagy. These variants illustrate how genetic background can amplify oxidative injury, cardiovascular risk, and renal decline [9].

Gene–Environment Interactions: Genetic susceptibility interacts with environmental and metabolic factors such as hypertension, hyperglycemia, and uremic toxin exposure to exacerbate OS and accelerate disease progression. Individuals harboring pro-oxidant polymorphisms may exhibit amplified ROS responses to common insults, underscoring the importance of personalized risk assessment.

Clinical Implications of Oxidative Stress in CKD

Renal Dysfunction Progression: Oxidative stress directly contributes to CKD progression by damaging glomerular, tubular, and interstitial structures. Excess ROS and RNS induce podocyte injury, mesangial expansion, and tubular epithelial apoptosis, promoting glomerulosclerosis and interstitial fibrosis. Profibrotic signaling pathways, including TGF-β, connective tissue growth factor, and NF-κB, are activated by ROS, resulting in extracellular matrix deposition and progressive nephron loss [3,4]. Clinical studies show that elevated

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oxidative biomarkers—such as malondialdehyde (MDA) and advanced oxidation protein products (AOPPs)—correlate with accelerated decline in estimated glomerular filtration rate (eGFR) independent of conventional risk factors [2].

Cardiovascular Disease and Endothelial Dysfunction: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD. Oxidative stress drives endothelial dysfunction, arterial stiffness, and vascular calcification by reducing nitric oxide bioavailability, promoting lipid peroxidation, and inducing chronic inflammation. Uremic toxins exacerbate this environment, fostering atherosclerotic plaque formation even in early CKD stages [6]. OS-mediated endothelial injury also increases susceptibility to hypertension and cardiac remodeling, linking renal pathology with systemic cardiovascular complications.

Anemia and Chronic Inflammation: CKD-associated anemia is partly attributable to oxidative stress. ROS damage erythrocyte membranes, shortening red blood cell lifespan, and impair iron metabolism by inducing hepcidin overexpression. Oxidative stress further suppresses erythropoietin responsiveness, complicating anemia management. Chronic low-grade inflammation, reinforced by ROS signaling, creates a vicious cycle that perpetuates renal injury and systemic complications [1].

Biomarkers of Oxidative Stress: Reliable biomarkers are essential for assessing OS in CKD, guiding prognosis, and monitoring therapeutic efficacy.

Lipid, Protein, and DNA Oxidation: Common biomarkers include malondialdehyde (MDA), F2-isoprostanes, AOPPs, and 8-hydroxy-2’-deoxyguanosine (8-OHdG), reflecting oxidative damage to lipids, proteins, and DNA respectively. Elevated levels correlate with CKD severity, progression, and cardiovascular risk [15].

Antioxidant Capacity Markers: Reduced activity of endogenous antioxidants-superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)-is observed in CKD. Total antioxidant capacity assays provide a global estimate of redox imbalance and are inversely related to disease severity [7].

Therapeutic Strategies Targeting Oxidative Stress

Antioxidant Supplementation: Vitamins C and E, selenium, and N-acetylcysteine have been trialed as adjunctive therapies in CKD. While some studies report improved oxidative biomarkers, clinical outcomes remain inconsistent due to heterogeneity in dosage, patient characteristics, and stage of disease [9].

Pharmacological Interventions: Agents such as renin–angiotensin–aldosterone system inhibitors (RAASi), statins, and SGLT2 inhibitors exhibit pleiotropic antioxidant effects, reducing ROS generation and enhancing endothelial function. These interventions confer renoprotection beyond their hemodynamic or metabolic effects [1].

Emerging Therapies: Targeting mitochondrial dysfunction, enhancing Nrf2 signaling, and reducing uremic toxin burden are promising strategies. Novel compounds and small molecules aimed at restoring redox homeostasis are currently under clinical evaluation, with potential to personalize oxidative stress–directed therapy.

Discussion: Oxidative stress represents a central unifying mechanism in CKD, bridging molecular, genetic, and systemic pathology. Unlike traditional risk factors, OS operates at multiple levels: cellular signaling, mitochondrial energetics, endothelial function, and systemic inflammation. Its pervasive influence explains why CKD is associated with multiorgan complications, notably cardiovascular disease, anemia, and immune dysregulation.

Mitochondria, as both sources and targets of ROS, create a feedback loop in CKD. Early mitochondrial injury amplifies ROS production, further damaging mitochondrial DNA and

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impairing ATP generation. This vicious cycle contributes to tubular atrophy, interstitial fibrosis, and eventual nephron loss. Strategies that restore mitochondrial bioenergetics or promote mitophagy may break this cycle and attenuate disease progression [4].

Polymorphisms in antioxidant, inflammatory, and mitochondrial genes, such as HLA, Nrf2, and APOL1, modulate individual vulnerability to oxidative injury. Gene–environment interactions exacerbate redox imbalance, highlighting the importance of personalized approaches. For instance, APOL1 risk variants potentiate mitochondrial ROS production and podocyte apoptosis, explaining rapid progression in certain populations. Incorporating genetic profiling could enhance risk stratification and tailor antioxidant therapy [1,8].

OS in CKD is not confined to the kidney. Circulating ROS, uremic toxins, and inflammatory mediators promote vascular injury, endothelial dysfunction, and cardiac remodeling. This systemic dissemination necessitates holistic therapeutic approaches targeting multiple pathogenic pathways rather than single interventions.

Current clinical biomarkers inadequately reflect tissue-specific oxidative injury. Antioxidant therapies have yielded inconsistent results, likely due to variable bioavailability, disease heterogeneity, and timing of intervention. Future research should focus on:

1. Novel biomarkers for tissue-specific OS detection.
2. Targeted antioxidant strategies based on genetic and molecular profiling.
3. Combination therapies addressing mitochondrial dysfunction, NADPH oxidase inhibition, and uremic toxin removal.
4. Longitudinal clinical trials to evaluate efficacy and safety of emerging OS-directed interventions.

By integrating molecular, genetic, and clinical insights, precision medicine approaches can optimize early diagnosis, risk stratification, and therapy in CKD.

Conclusion: Oxidative stress is a pivotal mediator of CKD progression and systemic complications. Mechanisms include mitochondrial dysfunction, NADPH oxidase activation, uremic toxin accumulation, and endothelial dysregulation, modulated by genetic susceptibility. Biomarkers of oxidative damage provide insights into disease severity and therapeutic response, while antioxidant and pharmacologic strategies offer potential renoprotection. A comprehensive understanding of OS pathways can guide early diagnosis, personalized intervention, and improved patient outcomes in CKD.

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